



Pest Management Solutions for
Specialty Crops and Minor Uses

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October 15, 2020

Ms. Nancy Fitz
Minor Use Officer
US EPA OPP/Proc Desk (REGFEE)
Room S-4900
2777 S. Crystal Drive
Arlington, VA 22202

Dear Ms. Fitz:

Submission of the IR-4 oxytetracycline studies on olive and walnut

RE: Oxytetracycline
EAC™ Oxytetracycline Manufacturing Use Product, EPA Reg. No. 71185-5
FireLine™ 45 WP, EPA Reg. No. 80990-6

IR-4 Public Interest Finding:

- (1) The olive and walnut data being submitted was developed by IR-4.
- (2) The active ingredient, oxytetracycline, is already registered on other food crops.
- (3) The active ingredient/crop combination of PR #11876 oxytetracycline/walnut was pre-screened by EPA in 2016 and received a “yellow +++ light” by EPA since this product is an antibiotic and resistance issues must be addressed with CDC and FDA. The residue study was initiated in 2017. PR #11737 oxytetracycline/olive was pre-screened by EPA in 2018 and received a “yellow light” by EPA. The residue study was initiated in 2015. Reasons for why the uses on walnut and olive should be registered in the United States can be found below and in the accompanying benefits documents.
- (4) The use on olives is for a crop grown on less than 300,000 acres. There were a total of 37,500 acres of olives grown in the U.S. in 2019. The use on walnuts is for a crop grown on more than 300,000 acres. There were a total of 365,000 acres of walnuts grown in the U.S. in 2019. However, this product is needed for providing control of a major bacterial pathogen, *Xanthomonas arboricola* pv. *juglandis* (walnut blight) affecting walnut production. Oxytetracycline provides a new, efficacious mode of action (FRAC Code 41) against this pathogen. The California Walnut Industry is dependent on new products, as there is currently overuse and dependency on copper that has led to widespread copper (FRAC Code M1) resistance in many populations of the walnut blight pathogen in different growing regions of California. In addition, the other major product used, mancozeb (FRAC Code M3), is being cancelled soon in the European Union. This is a major issue for the California Walnut Industry since approximately 38% of California walnuts are marketed in the EU. Other than copper, the only other registered product for walnut blight is kasugamycin (FRAC Code 24). The biological

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and natural product controls that are currently registered for use on walnut can only reduce the walnut blight pathogen when there is low disease pressure. However, these treatments do not eliminate the pathogen. Therefore, growers do not prefer to use these products because if a walnut blight outbreak occurs, the pathogen will contaminate the buds and establish as twig cankers, resulting in high levels of disease. The registration of oxytetracycline can play a significant role in integrated pest management since oxytetracycline shows high toxicity to copper-resistant strains of the walnut blight pathogen, it shows high efficacy of control in the lab and field of the pathogen, it has a different mode of action than what is currently registered, it degrades rapidly in the sun, it has extremely low persistence in the environment, it has high-binding properties to soil particles, rendering the molecule biologically inactive once in the soil and oxytetracycline does not select for resistance in non-target human bacteria with agricultural field usage.

A registration of oxytetracycline (marketed as FireLine™ 45 WP Fungicide/Bactericide by AgroSource, Inc.) on walnut and olive can provide a number of benefits for control of Walnut Blight (*Xanthomonas arboricola* pv. *juglandis*) in walnut and Olive Knot (*Pseudomonas savastanoi* pv. *savastanoi*) in olive. These uses would greatly support the Walnut Industry of California, The Olive Growers Council of California and the Olive Oil Commission of California. This fungicide/bactericide, which is in FRAC group 41, has been registered for many years on other food crops including apples and pears for the management of fire blight (*Erwinia amylovora*), and peaches and nectarines for the management of bacterial spot (*Xanthomonas campestris* pv. *pruni*). The pesticidal use of oxytetracycline on plants is small compared to the animal and human usage and represents a small fraction of all uses of oxytetracycline. Oxytetracycline has been used in plant agriculture for over 30 years without any documented evidence of human health effects. Oxytetracycline is produced naturally by *Streptomyces rimosus*. It is a reversible bacteriostat that inhibits protein synthesis at the ribosome. Oxytetracycline has a short residual life. This was demonstrated in the IR-4 residue studies PR 11737 (olive) and PR 11876 (walnut). In walnut, when oxytetracycline was applied at 1.5 pounds product per acre at a range of 100-150 gallons per acre as three foliar directed airblast applications starting at pistillate flower emergence at 6 to 10 day re-treatment intervals, followed by a fourth foliar directed airblast application 59 to 62 days before harvest (59 to 62 day PHI), resulting residues were <LLMV (less than 0.1 ppm). In olive, when oxytetracycline was applied at 1.0 pound product per acre at 100 gallons per acre as three foliar directed airblast applications starting in early to mid-February at 27 to 35 day intervals, followed by a fourth foliar directed airblast application 113 to 128 days before harvest (113 to 128 day PHI), resulting residues were <LLMV (less than 0.1 ppm). Product performance data with oxytetracycline has proven that this compound provides good control of Olive Knot and Walnut Blight when it is rotated with other effective compounds. This is beneficial since copper resistance is becoming widespread in both olive and walnut production. Please note that this submission also contains a Benefits Discussion and Rationale Supporting the Addition of Olives and Walnuts to the Section 3 Label for FireLine™ 45 WP (Oxytetracycline Hydrochloride) and also support letters from the University of California, The California Walnut Commission, The Olive Growers Council of California and the Olive Oil Commission of California.

In walnut, the use of oxytetracycline to control Walnut Blight would provide an excellent Integrated Pest Management Fit since it can be easily integrated into the grower's disease management program, while reducing the total load of other registered fungicides/bactericides applied to the environment, including copper (FRAC Code M1), mancozeb (FRAC Code M3) and kasugamycin (FRAC Code 24). Currently, these are the only registered products that are efficacious on walnut blight, which occurs throughout the state of California. Registering alternative modes of action are important since overuse and dependency on copper has resulted in widespread copper resistance in many populations of the walnut blight pathogen in different growing regions of California. In addition, large quantities of mancozeb are being applied. If registered, oxytetracycline would be an excellent rotation partner to help

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prevent overuse and selection of resistance of other registered products including copper products and mancozeb. Currently, copper-mancozeb is the most effective treatment followed by kasugamycin-mancozeb or kasugamycin-copper tank mixtures to manage copper-resistant pathogen populations. However, mancozeb will be cancelled in the EU over the next few years. This is a major issue since approximately 38% of California walnuts are marketed in the EU. The use of biological and natural products can reduce disease under low pressure. However, these products are ineffective under high disease pressure. Once a major outbreak of the pathogen occurs, it contaminates the buds and becomes established as twig cankers, taking several years to eradicate with the available conventional products (copper, mancozeb and kasugamycin). Oxytetracycline shows high efficacy against copper resistant strains, rapidly degrades in the sun, has extremely low persistence in the environment, is biologically inactive once in the soil and does not select for resistance in non-target human bacteria with agricultural field usage. Oxytetracycline has a four-application limit per year and will be used in rotation with other registered products. It will also have a long PHI of 60 days.

In olive, the use of oxytetracycline would provide an Integrated Pest Management Fit since it can serve as a rotation partner with copper. Olive knot occurs throughout the state and there is a major need to register alternative modes of action for control against bacterial pathogens. Like walnut, there is an overuse and dependency on copper. This has led to the first detection of copper resistance in the state recently. Copper is the only efficacious product registered to control olive knot. Another registered product, Gallex, is phytotoxic and has to be applied by hand to individual injuries. Biological and natural product controls only reduce disease under low pressure. They are ineffective under high disease pressure. Oxytetracycline shows high toxicity to copper-resistant strains of the pathogen in the lab and field. Use of oxytetracycline after the harvest season, during dormancy and the early spring period would allow applications to be applied before flowering and fruiting. The use of oxytetracycline is also important since the cultivar Arbequina, which is the primary cultivar grown for oil production in California, is highly susceptible to olive knot infection.

New Uses	Supporting Data	
Tolerances Requested	IR-4 PR Number	Source of New Tolerance
Walnut, black Walnut, English	11876	IR-4 walnut residue data
Olive	11737	IR-4 olive residue data

Fee Category: R-170 x 2

Registration Fee: \$83,317 each (See IR-4 Exemption Request Below)

The undersigned, Kathryn Homa, Fungicide Coordinator, Interregional Research Project No. 4, The State University of New Jersey, Princeton, New Jersey 08540, on behalf of the IR-4 Project and the Agricultural Experiment Station of the state of California submits this petition pursuant to Section 408(e) of the Federal Food, Drug and Cosmetic Act, as amended, with respect to the pesticide chemical, oxytetracycline (40 CFR 180.337).

As per the Pesticide Registration Improvement Act, the IR-4 tolerance petition for oxytetracycline (40 CFR 180.337) in/on walnut and olive is in the public interest and therefore exempt from the registration services fee. IR-4 in cooperation with the registrant AgroSource, Inc. (registrant for FireLine™ 45 WP) and Geo Logic Corporation (registrant for EAC™ Oxytetracycline Manufacturing Use Product) requests an exemption of the registration services fee for this tolerance petition.

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List of Studies Submitted with this letter in Support of Proposed Tolerances for oxytetracycline (40 CFR 180.337) in/on walnut and olive.

Vol. #	Volume Title	MRID No. / PP No.
1	Petition (Administrative Volume) Proposing Tolerances For Oxytetracycline Use in the Production of Walnut and Olive	---
2	Oxytetracycline: Magnitude of the Residue on Walnut (PR 11876)	51055401
3	Oxytetracycline: Magnitude of the Residue on Olive (PR 11737)	51055402

The entire submission is being made as an electronic submission only using EPA's CDX Pesticide Submission Portal (PSP).

Enclosed in this submission are the Administrative Volume, the Data Volumes, Notice of Filing, the Letter of Authorization from AgroSource, Inc. (dated August 25, 2020) and Geo Logic Corporation (dated August 25, 2020) and the following listed below:

For the technical product:

- EPA Form 8570-1 for EACTM Oxytetracycline Manufacturing Use Product (EPA Reg. No. 71185-5)
- EPA Form 8570-34 Certification with Respect to Citation of Data for EACTM Oxytetracycline Manufacturing Use Product (EPA Reg. No. 71185-5)
- EPA Form 8570-35 Data Matrix (EPA copy) for EACTM Oxytetracycline Manufacturing Use Product (EPA Reg. No. 71185-5)
- EPA Form 8570-35 Data Matrix (Public copy) for EACTM Oxytetracycline Manufacturing Use Product (EPA Reg. No. 71185-5)
- EACTM Oxytetracycline Manufacturing Use Product label Redline Copy (EPA Reg. No. 71185-5)
- EACTM Oxytetracycline Manufacturing Use Product label Black Copy (EPA Reg. No. 71185-5)

For the FireLineTM 45 WP end use product:

- EPA Form 8570-1 Application for Pesticide for FireLineTM 45 WP (EPA Reg. No. 80990-6)
- EPA Form 8570-34 Certification with Respect to Citation of Data for FireLineTM 45 WP (EPA Reg. No. 80990-6)
- EPA Form 8570-35 Data Matrix (EPA copy) for FireLineTM 45 WP (EPA Reg. No. 80990-6)
- EPA Form 8570-35 Data Matrix (Public copy) for FireLineTM 45 WP (EPA Reg. No. 80990-6)
- Proposed Section 3 label for FireLineTM 45 WP Redline Copy (EPA Reg. No. 80990-6)
- Proposed Section 3 label for FireLineTM 45 WP Black Copy (EPA Reg. No. 80990-6)

Additional Documents Included in the IR-4 Submission are listed below:

- Benefits Discussion and Rationale Supporting the Addition of Walnuts to the Section 3 Label For FireLineTM 45 WP (Oxytetracycline Hydrochloride), MRID #512441-03
- Benefits Discussion and Rationale Supporting the Addition of Olives to the Section 3 Label for FireLineTM 45 WP (Oxytetracycline Hydrochloride), MRID #512441-06

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- Letter of Support from Dr. J. E. Adaskaveg for oxytetracycline on walnuts
- Letter of Support from Dr. J. E. Adaskaveg for oxytetracycline on olives
- Letter of Support from the Olive Growers Council of California
- Letter of Support from the Olive Oil Commission of California
- Letter of Support from the California Walnut Commission
- FDA #152 Resistance Risk Assessment for Foliar Applications of FireLine™ 45 WP (active ingredient, Oxytetracycline Hydrochloride) to Walnuts, MRID #512441-02
- FDA #152 Resistance Risk Assessment for Foliar Applications of FireLine™ 45 WP (active ingredient, Oxytetracycline Hydrochloride) to Olives, MRID #512441-05

Please note that the following studies have already been submitted to EPA pertaining to the IR-4 submission of oxytetracycline on olive and walnut:

- MRID: 512441-01 Oxytetracycline: Exposure and Risk Assessments for a Proposed New Use on Walnuts and New Tolerances
- MRID: 512441-02 FDA #152 Resistance Risk Assessment for Foliar Applications of FireLine™ 45 WP (active ingredient, Oxytetracycline Hydrochloride) to Walnuts
- MRID: 512441-03 Benefits Discussion and Rationale Supporting the Addition of Walnuts to the Section 3 Label For FireLine™ 45 WP (Oxytetracycline Hydrochloride)
- MRID: 512441-04 Oxytetracycline: Exposure and Risk Assessments for a Proposed New Use on Olives and New Tolerances
- MRID: 512441-05 FDA #152 Resistance Risk Assessment for Foliar Applications of FireLine™ 45 WP (active ingredient, Oxytetracycline Hydrochloride) to Olives
- MRID: 512441-06 Benefits Discussion and Rationale Supporting the Addition of Olives to the Section 3 Label for FireLine™ 45 WP (Oxytetracycline Hydrochloride)

The neurotoxicity study requirement (870.6200) was waived for oxytetracycline (HED Chapter of the Tolerance Reregistration Eligibility Decision Document (TRED) and Proposed New Uses on Apples. Revised After Phase 3 Public Comment Period. 19-June-2006).

For the immunotoxicity study requirement, the following immunotoxicity study was submitted: MRID 48759601 for oxytetracycline.

Please see the following table for a comparison of tolerances / MRLs (in mg/Kg or ppm). There are no Codex or Canadian tolerances for oxytetracycline according to <https://www.globalmrl.com/db#query>

Commodity	U.S. (ppm)	Canada (ppm)	Codex (mg/Kg)
Walnut, black	0.1 (proposed) ¹	---	---
Walnut, English	0.1 (proposed) ¹	---	---
Olive	0.1 (proposed) ²	---	---

¹ Tolerance based on calculation using the OECD Calculator on IR-4 walnut residue data.

² Tolerance based on calculation using the OECD Calculator on IR-4 olive residue data.

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IR-4 is requesting a tolerance on olive rather than Tropical and subtropical, small fruit, edible peel, subgroup 23A since the specific need was for olive.

This is also the reason why crop group updates for oxytetracycline were not requested for this submission.

For questions pertaining to the 8570 forms, the labels and the notice of filing, please contact Robert Jones, Agent for Geo Logic Corporation and AgroSource, Inc., email: rejones@delta-ac.com. For questions concerning the transmittal letter, petition and / or final study reports, please contact Kathryn Homa, IR-4, Tel. No.: (732) 932-9575 ext. 4604; email: homa@njaes.rutgers.edu.

Yours very truly,
Interregional Research Project No. 4
Petitioner

Per 

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Rene.Amundson@AgroSource.net; (Uploaded letter, administrative & data volumes)
IR-4 Regional Coordinators (Uploaded letter & administrative volume)
Susan Bierbrunner, Ken Samoil, Debbie Carpenter, Dan Kunkel (IR-4, letter only)

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